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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/650,592	08/27/2003	Noubar B. Afeyan	COTH-P01-001	7920

56155 7590 08/05/2008

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EXAMINER	
MEAH, MOHAMMAD Y	

ART UNIT	PAPER NUMBER
1652	

MAIL DATE	DELIVERY MODE
08/05/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/650,592	AFEYAN ET AL.	
	Examiner	Art Unit	
	MD. YOUNUS MEAH	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 May 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *5 and 7-9, 26, 27, 29, 31, 35, 37, 48-51, 58, 69-70, 72, 74, 76, 78, 108, 117, 127-129, 131-134, 156 and 157* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/5/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 5,7-9,26,27,29,31,35,37,48-51,58,69,70,72,74,76,78,108,117,127-129,131-134,156 and 157.

DETAILED ACTION

Claims 5, 7-9, 26, 27, 29, 31, 35, 37, 48-51, 56, 58, 69-70, 72, 74, 76, 78, 108, 110, 117, 127-129, 131-135, 137, 147, 150, 156 and 157 are pending. With supplemental amendment of this application, the applicants, on 05/5/ 2008, argue on the rejection of claims 5 and 7-9, 26, 27, 29, 31, 35, 37, 48-51, 58, 69-70, 72, 74, 76, 78, 108, 117, 127-129, 131-134, 156 and 157, amended claims 5,108 and cancelled claim 107. Claims 56, 110, 135, 137, 147 and 150 remain withdrawn. Claims 5 and 7-9, 26, 27, 29, 31, 35, 37, 48-51, 58, 69-70, 72, 74, 76, 78, 108, 117, 127-129, 131-134, 156 and 157 will be examined.

Specification Objection

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code at paragraphs 0360 and 0602. See MPEP § 608.01.

Sequence compliance

Applicant is required to comply with the sequence rules by inserting the sequence identification numbers of all sequences recited within the claims and/or specification. It is particularly noted that variety of sequences are recited in the specification without giving any sequence listing. Appropriate correction is required. See particularly 37 CFR 1.821(d).

Claim Rejections

35 U.S.C 112

35 USC 112 2nd paragraph

Rejection of claims 5 and 7-9, 26, 27, 29, 31, 35, 37, 48-51, 58, 69-70, 72, 74, 76, 78, 108, 117, 127-129, 131-134, 150, 156 and 157 (dependent on claim 5) under 35 USC 112 2nd paragraph is withdrawn after amendment of the claim 5.

35 USC 112 1st *paragraph*

Rejection of claims 5 and 7-9, 26, 27, 29, 31, 35, 37, 48-51, 58, 69-70, 72, 74, 76, 78, 108, 117, 127-129, 131-134, 150, 156 and 157 (dependent on claim 5) under both 35 USC 112 1st paragraph written description and enablement rejection is withdrawn after amendment of the claim 5.

CLAIM Rejection - 35 U.S.C 102

Claims 5 and 7-9, 26, 27, 31, 37, 69-70, 72, 74, 78, 108, 117, 127-129, 150, 156 and 157 are rejected under 35 U.S.C. 102(b) as being anticipated by Davis et al. (WO 00/64485).

Davis et al. teach fusion proteins wherein enzymes (serine protease, chymotrypsin, matrix metalloproteinase, etc) which catalyse the degradation of a target wherein said target comprise blood stains (i.e, insoluble protein-containing

aggregate) , milk stain, etc (Paragraph 0067) conjugated to binding partners wherein the binding partner is ligand binding domain or protein or peptide or antibody (i.e., immunoglobulin, Fab, $F(ab)_2$) to the target with or without a linker and resulting fusion protein has greater (catalytic or more than one) activity than the unconjugated molecule . The chimeric protein of Davis et al. bind to the target and alter (degrade) a wide variety of protein or polypeptide substrate (receptors and/or intermediary signaling molecules such as cytokines, EGF-like factors, blood stain (insoluble protein-containing aggregate) wherein the protease (such as serine hydrolase, paragraphs 0014-0025) portion of the chimeric molecule used to make the chimeric protein hydrolyses peptide bond of substrate polypeptide or protein on a insoluble protein-containing aggregate (i.e., blood stain) by catalyzing the proteolytic cleavage of the said substrate polypeptide to produce one or more products (inherent property of protease, such as serine hydrolase). . Davis et al. use the fusion protein as a pharmaceutical composition wherein the targeted enzyme is protease (trypsin, chymotrypsin) and use the pharmaceutical composition for autoimmune disease, infectious diseases, cancer, etc. In the prior action of date 2/5/08 35 U.S.C. 102(b) rejection as being anticipated by Davis et al. (WO 00/64485) was withdrawn because biological accretion moiety was considered as dead protein or dead cell, however, as applicant amended claim 1 by replacing biological accretion by insoluble protein-containing aggregate, the rejection is brought back.

Claims 5 and 7-9, 26, 27, 37, 69-70, 72, 74, 78, 108, 117, 127-129, 150, 156 and 157 are rejected under 35 U.S.C. 102(b) as being anticipated by Holvoet et al. (JBC1991, vol.266, pp 19717-19724).

Holvoet et al. teach (page 1 paragraph 1 and 2) fusion proteins of plasminogen activator (Urokinase – a serine protease) fused with a fibrin-specific antibody (variable region Fv) molecule. The resulting fusion protein shows 2.5-fold increase of the fibrinolytic potency. This fusion protein targets a blood clot then cleaves plasminogen to release active plasmin (an enzyme) resulting plasmin in turn digests or lyse clot. In the prior action of date 2/5/08 35 U.S.C. 102(b) rejection as being anticipated by Holvoet et al. was withdrawn because biological accretion moiety was considered as dead protein or dead cell, however, as applicant amended claim 1 by replacing biological accretion by insoluble protein-containing aggregate, the rejection is brought back.

CLAIM Rejection - 35 U.S.C 103a

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 5 and 7-9, 26, 27, 35 37, 69-70, 72, 74, 78, 108, 117, 127-129, 150, 156 and 157 are rejected under 35 U.S.C. 103(a) by Davis et al. (WO 00/64485) in view of, Bhatia et al (Intl. J. Cancer 2000, 85, 571-57). Davis et al.

teach fusion proteins wherein enzymes (serine protease, chymotrypsin, matrix metalloproteinase, etc) which catalyse the degradation of a target wherein said target comprise blood stains (i.e., insoluble protein-containing aggregate) , milk stain, etc (Paragraph 0067) conjugated to binding partners wherein the binding partner is ligand binding domain or protein or peptide or antibody (i.e., immunoglobulin, Fab, $F(ab)_2$) to the target with or without a linker and resulting fusion protein has greater (catalytic or more than one) activity than the unconjugated molecule . The chimeric protein of Davis et al. bind to the target and alter (antagonize/inhibit/degrade) a wide variety of protein or polypeptide substrate (receptors and/or intermediary signaling molecules such as cytokines, EGF-like factors, blood stain (insoluble protein-containing aggregate) wherein protease (such as serine hydrolase, paragraphs 0014-0025) portion of chimeric molecule used to make the chimeric protein hydrolyses peptide bond of substrate polypeptide or protein on a insoluble protein-containing aggregate by catalyzing the proteolytic cleavage of the said substrate polypeptide to produce one or more products (inherent property of protease, such as serine hydrolase). Davis et al. use the fusion protein as a pharmaceutical composition wherein the targeted enzyme is protease (trypsin, chymotrypsin) and use the pharmaceutical composition for autoimmune disease, infectious diseases , cancer, etc. Davis et al. chimeric protein is chemically cross-linked fusion protein not a fusion protein made by cotranslation of respective genes.

Protein conjugates can be made either by chemical conjugation or by gene fusion methods but gene fusion methods have some particular advantages

(see last paragraph of column one of page 571 of Bhatia et al Intl. J. Cancer 2000, 85, 571-577). It is well known in the prior art how to make fusion proteins by translation of a chimeric gene fusion (such as references supplied in the amendment by the applicants and also Bhatia et al Intl. J. Cancer 2000, 85, 571-577). Bhatia et al teach antibody-targeted enzymes made by gene fusion method. Therefore, one knowledgeable in prior art is **motivated** to make the protein conjugate of Davis et al by gene fusion methodology as taught by Bhatia et al.

As such it would have been obvious to one of ordinary skill in the art to make the fusion protein (such as, serine protease conjugated to antibody) of Davis et al. by the method Bhatia et al. and use the resulting adzyme to cleave or degrade substrate polypeptide or protein on an insoluble protein-containing aggregate by catalyzing the proteolytic cleavage of the said substrate polypeptide.

Claims 29, 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Davis et al. (WO 00/64485), in view of Bhatia et al (Intl. J. Cancer 2000, 85, 571-57) as applied to claims 5 and 7-9, 26, 27, 37, 69-70, 72, 74, 78, 108, 117, 127-129, 150, 156 and 157 above, and further in view of Guo et al. (Biotech. and Bioeng. 2000, 70, 456-463).

Davis et al. teach fusion proteins wherein enzymes (serine protease, chymotrypsin, etc) which catalyze degradation of a specific target are conjugated to binding partners wherein the binding partner is an antibody (immunoglobulin)

through **a linker but not** through Gly_4Ser type of linker. Bhattia et al. is described above.

Guo et al. teach fusion proteins wherein an enzyme (ASNase) is conjugated to a immunoglobulin or fragment or antibody (scFV) by a linker polypeptide $(Gly_4Ser)_3$.

As such it would have been obvious to one of ordinary skill in the art to make the fusion protein (such as, serine protease conjugated to antibody) of Davis et al. by the method Bhatia et al wherein serine protease is conjugated to antibody via a linker as taught by Guo et al. and use the resulting adzyme to cleave or degrade substrate polypeptide or protein on a insoluble protein-containing aggregate by catalyzing the proteolytic cleavage of the said substrate polypeptide

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Double Patenting Rejection

Provisional rejection of claims 5, 7-9, 26-27, 29, 31, 35, 37, 52-53, 58, 69-70, 72, 74, 76, 78, 108, 119 and 127-29, 131-134, are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 4-5, 30-34 37-41 of copending Applications No.10792498 and 10650591 is remain.

Examiner agrees with applicant that the provisional obviousness-type double patenting rejections may be withdrawn when all claims are otherwise allowable if the copending application is not allowed (however see MPEP 804 I(B)(1) for situations where this may not be the case) or when applicants submit a terminal disclaimer, however until one of these conditions apply the rejections will be maintained.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mohammad Meah whose telephone number is 571-272-1261. The examiner can normally be reached on 8:30-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Nashaat T. Nashed can be reached on 571-272-0934. The fax phone number for the organization where this application or proceeding is assigned is 571-272-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see **http://pair-direct.uspto.gov**. Should you have questions on access to the Private PAIR

system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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